

A HEPATITIS VIRUS OF MICE.

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DURING the autumn of 1950 considerable losses were experienced in the breeding stock of a strain of white mice (Parkes (P) strain) maintained at the National Institute for Medical Research. Owing to structural repairs to the animal house, the P mice had been confined to half the space normally allotted to them, and central heating was temporarily unavailable. The majority of dead mice had massive caseous lesions of the liver, a substantial minority had the liver lesions characteristic of infection with *Bacillus piliformis* and a few had indefinite lesions. From the caseous liver lesions were isolated Gram-positive organisms, possibly enterococci. While intraperitoneal injection of mice with cultures of these organisms occasionally reproduced the caseous liver lesions, feeding cultures regularly failed to do so. It therefore seemed possible that the primary causal agent might be a virus which damaged the liver sufficiently to render it susceptible to a variety of secondary invaders. Accordingly, membrane filtrates of liver extract from dead P mice were passed as described below in young weaned mice of another (VS) strain maintained at the Institute, since it was felt that the P mice might have become immune to any agent originally responsible for the outbreak. This VS strain of mice originated from the Rockefeller albino mice selectively bred by Webster (1937) for resistance to bacteria and susceptibility to viruses. By the fourth pass, liver lesions were quite evident at one week in killed VS mice and by the fifth pass there were deaths. The infective agent will be termed mouse hepatitis virus (MHV).

The purpose of this communication is to give some account of the disease produced in mice by MHV and to describe its general properties.

TECHNIQUE.

Extracts of liver and kidneys were prepared from sick or moribund mice infected 5 or 6 days previously by mincing the organs and grinding with sterile powdered glass or quartz with pestle and mortar. The tissue emulsion was suspended in 5 or 10 per cent horse serum broth—5 ml. for the pooled liver and kidneys of one mouse. After sedimentation by gravity or light centrifugation to remove the coarser particles, the supernatant was ready for use. All dilutions were made in serum broth, the dose per mouse being from 0.15 ml. to 0.30 ml. of ten-fold dilutions of the extract.

For filtration, the crude extract was centrifuged for 10 min. at 3000 r.p.m. and filtered by positive pressure through a 2.0 μ A.P.D. (average pore diameter) gradocol membrane, followed by filtration through a 1.0 μ upon a 0.7 μ membrane. Such filtrates proved bacteriologically sterile, nor was it possible to grow from them organisms of the pleuro-pneumonia group.

Newly weaned VS mice of 8–11 g. (aged 3–4 weeks) infected by intraperitonea inoculation proved to be the most convenient and sensitive indicator for the presence of MHV and were generally used for this purpose.

THE DISEASE IN MICE.

The symptoms in affected mice.—Infected VS mice (8–11 g.) appear slightly unwell after an incubation period varying from 4 to 7 days according to the magnitude of the infecting dose. Thereafter, the mice rapidly deteriorate, becoming very ill, often with muscular tremors; if twisted by the tail they may go into a tonic spasm and die. The urine is markedly yellow, red or brown, staining the coat in the perineal region. Mice becoming very ill die within a few hours, but slightly ill mice may recover. The mortality in VS mice of less than 14 g. weight approaches 100 per cent, the highest death-rate occurring on the fifth day after infection with a heavy dose, on the seventh or eighth day with a dose which is only just lethal.

The macroscopic lesions in mice.—On post-mortem examination the most striking abnormality is found in the liver. This is swollen and friable; it may be pale yellow and mottled with petechial haemorrhages, or it may be brown and similarly mottled. Its appearances do, in fact, simulate those associated with ectromelia. The spleen is often somewhat swollen and dark in colour. The kidneys may be swollen and pale, especially in the more chronic cases. Susceptible mice infected with a small dose and showing no definite symptoms of illness frequently manifest striking liver lesions if killed between the seventh and tenth day after infection. In mice which appear to have recovered the liver presents an irregular surface as if there were uneven shrinkage of fibrous tissue.

Histological changes.—Only preliminary observations on histology have yet been made. The earliest liver lesions have been found 3 days after intraperitoneal inoculation; they take the form of small round cytoplasmic inclusion bodies in cells of liver parenchyma; they are pink in tissue stained with haematoxylin and eosin. Study of sections obtained on subsequent days suggests that the inclusions rapidly enlarge, and that the cytoplasm is soon filled by deeply eosinophilic material. Since necrotic liver cells may in any case become eosinophilic, it is hard to say how far all the deeply pink-staining material is of the same nature as the inclusions observed earlier. At the same time, degenerative nuclear changes occur, first margination of chromatin and then nuclear fragmentation. The affected cells appear to run together, forming deep pink masses. These focal necroses are scattered through the liver substance; they may or may not be in close relationship to blood vessels. Infrequently, intranuclear inclusions have been found in numbers; they may be due, not to the same agent, but to that described by Findlay (1932) and by Pavlanis and Lépine (1949). In mice which die the liver necrosis extends until little recognisable structure remains. In those which recover a cellular reaction rapidly sets in. Polymorphs and mononuclear cells appear in the foci; the masses of pink material shrink and are walled off by giant cells; proliferation of bile ducts is very active and mitoses of hepatic cells are numerous. After 15 days livers of recovered mice may show a diffuse proliferation of young connective tissue, largely intercellular, but showing at times a coarser architecture.

In some mice pink cytoplasmic inclusions, together with some epithelial necrosis, have been found in kidney tubules. Gross kidney damage has been

rare, though occasionally very extensive in older P mice. Focal meningeal lesions have been seen, but systematic histological study has still to be carried out.

Properties of the Virus.

The LD₅₀ and size of MHV.—The LD₅₀ of liver-kidney extract was determined by the method of Reed and Muench (1938) from the mortality amongst groups of VS mice (8–11 g.) inoculated intraperitoneally with ten-fold dilutions from 10⁰ to 10⁻⁶; it was within the range of 10⁻⁴ to 10⁻⁵ ml. both for unfiltered extracts and for filtrates through membranes of A.P.D. 0.7–0.8 μ . Using such filtrates for filtration through finer membranes, we found that the virus would pass through 0.35 μ and 0.3 μ membranes, but failed to pass through membranes of 0.25 μ . The protocols of these experiments are given in Table I. These results indicate that MHV is one of the larger viruses, falling in the range 130–180 m μ ; it is, therefore, of about the same size as vaccinia. It may also be observed in Table I that the average survival time increases somewhat regularly with increasing dilution of virus.

TABLE I.—*The Filterability of MHV.*

*APD of membrane filter.	Dose injected i/p (ml.).	Numbers dying.	Average survival time of mice which died (days).
0.75 μ	0.25 \times 10 ⁻⁶	0/5	—
"	0.25 \times 10 ⁻⁵	1/6	8
"	0.25 \times 10 ⁻⁴	1/6	8
"	0.25 \times 10 ⁻³	3/6	7.3
"	0.25 \times 10 ⁻²	6/6	6.7
"	0.25 \times 10 ⁻¹	5/5	6.2
"	0.25 \times 10 ⁰	5/5 (6/6)	5.6 (5.0)
0.35 μ	0.3 \times 10 ⁰	5/5 (6/6)	7.0 (6.0)
0.30 μ	0.3 \times 10 ⁰	6/6	7.2
0.25 μ	0.3 \times 10 ⁰	0/5 (0/6)	— (-)

The LD₅₀ calculated from this experiment is 1.3 \times 10⁻⁴ ml.

The bracketed figures refer to a second filtration experiment.

* APD = average pore diameter of gradocol membrane filters.

The infectivity of blood, urine and faeces.—Blood drawn into heparin from the hearts of anaesthetized mice moribund of the disease proved infective, having an LD₅₀ certainly less than 1 ml. \times 10⁻² in one experiment and 2 ml. \times 10⁻³ in another. Urine obtained direct from the bladders of killed moribund mice infected a proportion of mice in a dose of 5 ml. \times 10⁻³ in one experiment. In three other experiments a dose of 3 ml. \times 10⁻² failed to infect any of 6 mice. A 0.7 μ membrane filtrate of extract prepared from faeces taken from the rectum of killed moribund mice proved infective for susceptible VS mice in two of three experiments. It thus seems that the blood of infected mice contains a relatively high concentration of virus, and that virus may be present in the faeces and occasionally in the urine.

Other routes of infecting mice.—Since nervous symptoms are sometimes shown by sick mice, we studied the effect of brain-to-brain passage of the virus in young VS mice to discover whether its neurotropism could be easily enhanced. It was found that, although the virus was maintained for four brain passes, the character of the disease produced did not vary. The lengthened time of survival (8–9 days) and the fact that some mice survived suggested that brain extract may have been infective on account of the blood contained in it. Young VS mice were also successfully infected by subcutaneous and intranasal inoculation. One attempt

has been made to infect mice by mixing about 10^4 LD₅₀ of MHV with the diet fed to 12 young VS mice on 3 consecutive days. Two mice died with typical lesions 12 and 13 days after the first feeding with virus. The disease did not pass from mouse to mouse by cage contact as a lethal infection. We are now studying the question of whether it does so as an inapparent immunizing infection.

Attempts to infect other laboratory animals.—Attempts were made to infect cotton-rats, guinea-pigs and hamsters by intraperitoneal inoculation of a maximum amount of active extract; no symptoms or lesions were produced in these species. Liver and kidney extract from two young rabbits infected with active virus was passed to susceptible mice and to further rabbits without apparent result. In rats, two litters of 2–4 days were infected by intraperitoneal injection, and liver-kidney extract from them was passed 7 days later to susceptible mice and two more litters of rats; no symptoms were observed within a period of a week after infection, at which time no lesions were observed in the killed mice or rats. The adaptability of the virus to rats is, however, still under investigation. Unsuccessful attempts were also made to infect cats, ferrets and a dog.

Attempts to grow the virus in fertile eggs and tissue cultures.—Unsuccessful attempts were made to infect fertile eggs by inoculation on to the chorio-allantoic membrane, into the yolk sac and into the allantoic cavity. Failure to produce symptoms or lesions in susceptible mice inoculated with material harvested from the eggs was taken as indicating absence of growth of the virus in the eggs. Inoculations were also made into the amnion of fertile eggs; lesions were not produced in mice by the amniotic fluid harvested from them except minimal lesions at the first pass; there was possibly some survival of the original inoculated virus. No growth or survival of virus has been obtained in tissue cultures, using chick and mouse embryos in Carrel flasks and roller tubes, by ourselves or by our colleague, Dr. T. H. Flewett.

Resistance of MHV.—The relative absence of resistance of the virus to heat, ether, 50 per cent glycerol and storage at -65° , as detailed in Table II, seem to distinguish it from human infectious hepatitis. Results of storage at -65° have, however, been more erratic than the table indicates. In a preliminary experiment freeze-dried liver mince and liver extract were practically inactive after 9 days' storage at 2° . The preservation of the virus by freeze-drying is, however, still under investigation.

Neutralization of MHV.—Experiments were conducted to see whether MHV was neutralized by the sera from recovered and hyperimmunized mice. Normal sera were obtained from groups of 12–20 mice of 18–20 g., bled out under chloroform anaesthesia. Two such batches were prepared in this way from VS mice and from P mice.

Hyperimmunized mice were prepared from survivors of groups of VS mice of 10–12 g. infected by intraperitoneal inoculation of virus, reinfected 7–14 days later with 0.5 ml. of undiluted, unfiltered, active liver-kidney extract and bled out 14–20 days later. Two such batches were prepared, the mice being bled out 14 days (S_1) and 20 days (S_2) after the last injection. S_3 was prepared by bleeding out the 6 survivors of a group of 12 (14–16 g.) young adult VS mice infected with 10^3 LD₅₀ 14 days before. S_4 was prepared by bleeding out the 13 survivors of a group of 15 fully grown VS mice infected with a similar dose 14 days before.

TABLE II.—*Stability of MHV.*

Treatment.	LD ₅₀ of untreated control extract.	LD ₅₀ of treated portion of same extract.	Remarks.
Heated to 56° for 30 min.: (1) (2)	<0.25 ml. × 10 ⁻² 0.25 ml. × 10 ⁻³	>0.25 ml. >0.25 ml.	Inactivated; no symptoms or lesions produced in mice by 0.25 ml.
Kept in contact with 20 per cent ether overnight at +2°	<0.25 ml. × 10 ⁻³	>0.25 ml.	Inactivated; 5/6 mice receiving 0.25 ml. had no symptoms or lesions. One died with inconclusive lesions.
Liver suspended in 50 per cent glycerol for 6 weeks at +2°	<0.25 ml. × 10 ⁻²	>0.25 ml.	Practically inactivated; 3/5 mice receiving 0.25 ml. had liver lesions from which one had died.
Stored at -65°; (a) For 9 days . (b) For 2 months .	1.3 ml. × 10 ⁻⁴ 1.3 ml. × 10 ⁻⁴	1 ml. × 10 ⁻⁴ 3 ml. × 10 ⁻³	Titre unchanged. Titre 1/23 original titre.

TABLE III.—*Neutralization of MHV by Normal and Immune Sera.*

*Death rates of mice infected with virus-serum mixtures containing LD₅₀s of virus as hereunder:

Serum.	10 ⁰ -10 ¹	10 ¹ -10 ²	10 ² -10 ³	10 ³ -10 ⁴
Normal VS serum . . .	3/5	5/5	n.t.	n.t.
Normal P serum . . .	3/5	5/5	n.t.	n.t.
Immune VS serum (S ₁) . .	0/6	0/6	n.t.	5/5
" " (S ₂) . .	1/5	5/5	n.t.	n.t.
" " (S ₃) . .	0/4	4/5	5/5	5/5
" " (S ₄) . .	0/5	1/5	3/4	5/5

Numerators represent mice which died, denominators total mice in group.

n.t. = not tested.

The dose of serum was 0.1 ml. per mouse mixed beforehand with the appropriate doses of virus.

* Control mice were inoculated with dilutions of virus without mouse serum and from the results with these the number of LD₅₀s of virus in the mixtures was calculated.

The method of carrying out the neutralization test was to mix 0.1 ml. of unheated normal or immune serum with 0.15 ml. of ten-fold dilutions of active extract and, after letting stand $\frac{1}{2}$ -1 $\frac{1}{2}$ hrs. at 2°, to inject each dilution intraperitoneally into groups of 5 or 6 susceptible VS mice (8-12 g. weight). The LD₅₀ of the active extract had to be determined at the same time owing to the lability of the virus.

It is clear from Table III that neutralizing antibody cannot be detected in the sera from normal VS or normal P mice by the method adopted. The sera, S₂ and S₃, from recovered and hyperimmunized VS mice show no significant amount of detectable antibody; S₁ and S₄ do show detectable antibody, although the amount is small. It seems, therefore, that the antibody response to MHV is slight, and this is in harmony with the fact that virus has been recovered from the blood of mature carrier P mice (see below).

Age and Strain Susceptibility in Mice.

It was soon noticed that the susceptibility of VS mice became much less after they had attained 14 g. in weight, that is, after about 4-5 weeks of age; also that the majority of newly weaned mice of the P strain did not succumb

to inoculation with a heavy dose. These findings were confirmed and extended to three other strains of mice, the C3H, the C57 (kindly supplied by Dr. J. Craigie), and a stock of Swiss mice, separate from the VS mice, which are maintained at the National Institute for Medical Research. These results are shown in Table IV.

TABLE IV.—*The Relationship of Mortality to Age and Strain of Mice.*

Strain of mice.	Mortality in mice aged—		
	2-4 days.	3-4 wks. (9-14 g.).	6 wks. or more (>16 g.)
VS	36/36 (100%)	186/193 (96%)	4/25 (16%)
P	38/57 (67%)	21/78 (27%)	3/20 (15%)
C ₃ H	6/6	4/15	n.t.
C ₅₇	5/5	4/15	n.t.
Swiss	n.t.	3/12	n.t.

n.t. = not tested.

Inoculated intraperitoneally with 0.1 to 0.02 ml. active liver-kidney extract.

It is apparent that VS mice were uniformly susceptible until they attained a weight of 14 g. Between 14-16 g. the mortality was 6/12 (a result not appearing in the table), and above 16 g. more than 80 per cent survived challenge. For P mice, while the resistance was least shortly after birth and increased with age, mice of all ages showed some resistance. The mortality in P mice of 3-4 weeks old has since shown some tendency to rise. In experiments performed between February and May, 1951, the mortality was 0/10, 1/6, 2/6, 0/6 and 1/15; while in experiments performed in late June and July, it was 13/30 and 4/5 respectively. Throughout the period there appeared to be no change in the virus as judged by results in young VS mice. The resistance of the other strains would seem to resemble that of P mice, although the data are scantier for them. At any rate, it seems that of the strains tested, only VS mice remain highly susceptible at weaning time and for the first week or so afterwards.

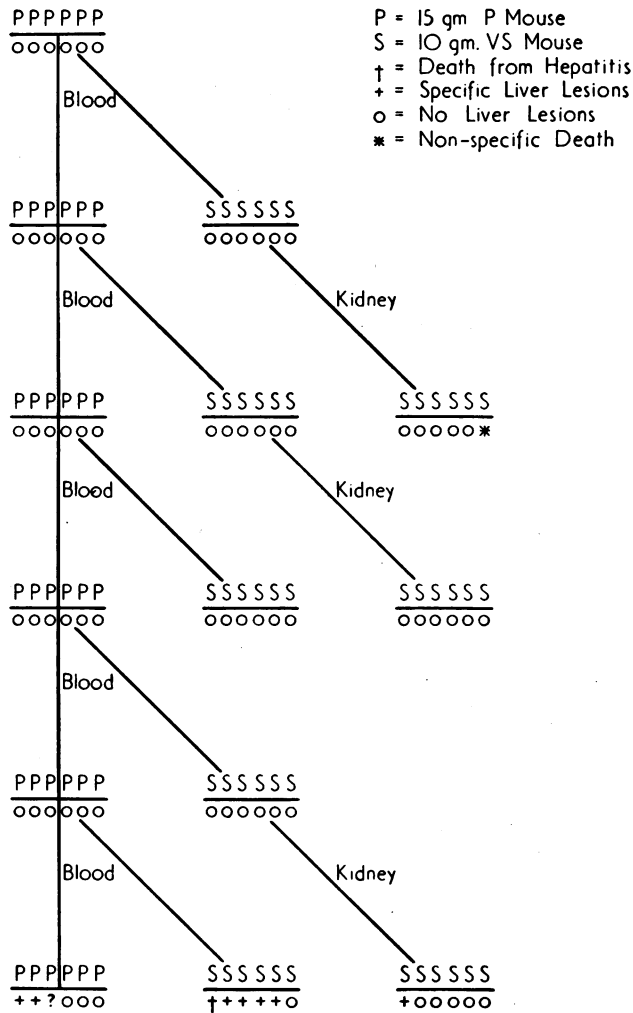
Activation of Latent Virus.

In the course of an endeavour to discover whence the mouse hepatitis virus came, the following experiments were carried out: Three normal P mice weighing about 15 g. were killed and their kidneys and livers ground separately in 10 per cent horse-serum broth to make approximately 10 per cent suspensions. Kidney suspension in 0.25 ml. quantity was inoculated intraperitoneally into 6 more P mice, and liver suspension similarly to 6 others. The mice were killed after 7 days and the procedure repeated. Two series were kept going, liver suspensions being used in one, kidney suspensions in the other. Three serial passages were thus carried out through P mice, but at the fourth pass VS mice were used instead. Eight days later 4/6 mice in the kidney series were dead with typical hepatitis, confirmed histologically, and a fifth had extensive liver lesions. Passage to further VS mice was successful. In the liver series 2/4 mice were dead with typical lesions after 8 days.

This experiment left it uncertain whether several serial passes through P mice were necessary, or whether at any stage passage to VS mice would have revealed virus activity. Accordingly, passages were made through P mice as before, with use of kidney suspensions only, and at each pass inoculation was made also into VS mice. In this experiment all mice, whether P or VS, remained negative until, as happened before, deaths from hepatitis occurred in VS mice after 4

passages. In a third trial, younger (10 g.) VS mice were used and only 3 passages were necessary to produce specific deaths; on this occasion all mice died at the third passage, both the 10 g. VS and the 15 g. P. One of the latter showed extensive necrosis of voluntary muscles, a picture not encountered otherwise.

RECOVERY OF VIRUS FROM BLOOD OF NORMAL P MICE



I. P. passage with blood or kidney suspension as shown,
at 7 day intervals.

FIGURE.

Next, kidney suspensions of normal P mice were injected intraperitoneally into 10 g. VS mice and serial passage carried on as usual but in young VS mice only. Hepatitis turned up after 3 passes.

Virus in blood of normal mice.

The possibility existed that passage from any organ might succeed because of presence of virus in blood of carrier mice. Heparinized heart blood of 6 normal P mice was therefore given intraperitoneally to 6 more P mice. These were bled after 7 days and passage thus carried on serially. No lesions appeared in the first 4 serial lots of P mice nor in the 10 g. VS mice which were subinoculated at each stage. But after 5 passes deaths from hepatitis occurred in both P and VS mice. Further details are contained in the figure.

Virus in faeces of normal mice.

Virus was recovered from filtered faeces of normal P mice after only one "blind passage" through young VS mice. In a further experiment faeces filtrates from 6 individual P mice were tested, but no infection was apparent in second-passages mice.

Do carriers exist in mice other than those of the P strain?

When starting material was a kidney suspension of normal 15 g. VS mice, 6 serial passages were carried out in such mice without revealing virus. A repetition of this test using 10 g. VS mice gave the same result (6 passes made at 5-day intervals). Similarly, no virus was activated after 4 passes when C₃H or C₅₇ mice were used to furnish starting material and for further passage.

Though deliberate cross-infection experiments have as yet given no conclusive results, occasional VS mice have succumbed to hepatitis under conditions suggesting a disease of different origin. We are therefore cautious in interpreting the above experiments, but inasmuch as "activation" experiments were conducted in a room free from other sources of infection, we feel justified in accepting most of the results at their face value. We thus tentatively conclude that mouse hepatitis virus is carried in the blood, liver, kidneys and faeces of apparently normal P mice; conceivably some organs are active only because of the blood they contain. The high susceptibility of young VS mice enables us to detect this carrier-state. Several passages through P or VS mice are necessary to reveal it. This might be (in the case of P mice) because the chances increase with every passage of encountering a carrier which would furnish virus; or because P mice resemble VS mice in that serial passage permits a trace of virus to increase in quantity or virulence. We have been able to show that mouse hepatitis virus multiplies in P mice after intraperitoneal inoculation, even when no lesions become evident; the second factor must therefore certainly play a part.

Recent experiments indicate that after intraperitoneal inoculation into P mice, virus is maximal in the kidneys after about 5 days. We may therefore have been waiting beyond the optimal time in making serial passes at weekly intervals.

Some Other Aspects of MHV.

Relationship of MHV to other viruses.—Of the viruses characteristically producing hepatitis in man and animals, MHV differs in its larger size, greater lability and in other ways from the viruses of yellow fever and rift valley fever. It differs from the viruses of infectious and homologous serum hepatitis of man in its short incubation period, its lability—notably its thermolability and its lack of resistance to ether, drying and storage at -60° . Fox encephalitis (Rubarth's

canine hepatitis) is also distinguished from MHV by the regular presence of intranuclear inclusion bodies and by different host specificities. There remain a number of reports of viral hepatitis in mice, either spontaneous or believed to have been produced with infectious material of human origin. Apart from the condition already mentioned characterized by an unusual type of intranuclear inclusion bodies (Findlay, 1932, and Pavilanis and Lépine, 1949), Nicolau and Ruge (1944) have described an agent believed to have derived from human infective jaundice and producing histological changes in mice. These changes do not resemble those produced by MHV. The liver lesions described in mice by Olitsky and Casals (1946) were detected histologically and did not make the mice evidently ill.

That MHV might be a variant of some already known virus with exaggerated hepatotropism must be reckoned as a possibility. Ectromelia produces liver lesions having a very close macroscopic resemblance to those of MHV; lymphocytic choriomeningitis and mouse disseminated encephalomyelitis (Cheever, Daniels, Pappenheimer and Bailey, 1949) are capable of producing liver lesions. MHV is distinguished from ectromelia by many properties such as its lability, its inability to produce a local lesion on the chorio-allantoic membranes of fertile eggs and on the footpads of mice, and its failure regularly to produce evident disease in older mice. It is distinguished from LCM by its narrow host specificity, by its lability, and also by the apparent difficulty of establishing it as a neurotropic virus. This absence of neurotropism at least distinguishes it from mouse disseminated encephalomyelitis. Other points of difference are that with the agent of the latter disease no inclusion bodies have been seen, it is not present in the blood of infected mice, and it is infective for hamsters, cotton-rats and rats.

The effect of chemotherapeutic agents upon infected mice.—Treatment with terramycin and aureomycin appears to prevent the development of hepatitis in mice infected with MHV. To a lesser extent chloromycetin and sulphamerazine exert a beneficial effect, while penicillin and streptomycin seem ineffective; streptomycin was tested both by injection and by feeding. The manner of action of these agents has not been elucidated; present indications are that the effect is a true chemotherapeutic action on the virus. This apparent susceptibility to chemotherapeutic agents might suggest that MHV is related to the psittacosis-LGV group of viruses and, although MHV is somewhat smaller than most of this group, its size falls within the range of the group. It differs from them in that it has not been demonstrated in preparations stained by Macchiavello's method, it will not grow in the yolk-sac of fertile eggs nor does it appear to be susceptible to penicillin.

DISCUSSION.

P mice appear to carry the mouse hepatitis virus and are relatively resistant. VS mice have not yet been proved to carry it but are highly susceptible, especially when young. There is thus an analogy between a lysogenic bacterium, itself insensitive to the phage it carries, and an "indicator organism" with the aid of which presence of the phage is revealed. In so far as suckling P mice and even older ones may be killed by the virus, it is doubtful whether we should press the analogy far. The cause of the greater resistance of P mice might be constitutional, or it might be consequent upon an acquired active immunity. The increased resistance of VS mice with age is less likely to depend upon an acquired active

immunity, since virus has not been recovered from this strain. The virus seems to multiply in adult VS mice, and often kills heavily pregnant animals. This suggests that the metabolic status of mice may be related to the symptoms observed in them.

Of special interest in relation to human hepatitis is the finding that apparently normal mice may carry the virus in the blood. We have already pointed out that in several respects, notably susceptibility to ether and to heat, mouse hepatitis virus differs from human hepatitis viruses.

The circumstances of discovery of the virus and some later observations suggest the possibility that the virus may play a part in some necrotic liver lesions in mice, normally attributed to infection with *B. piliformis* or other bacteria.

Finally, the unexpected finding of the preventive action of aureomycin and terramycin, taken together with earlier work on grey lung virus from this laboratory (Andrewes and Niven, 1950) shows that susceptibility to chemotherapy is not a property confined to the psittacosis group of viruses.

SUMMARY.

1. A virus (MHV) is described causing a fatal hepatitis in young mice.
2. MHV was present in the liver, blood, kidneys, faeces and urine of infected mice.
3. The virus differs from human hepatitis viruses in its lability and the short incubation period of the infection.
4. One strain of mice (VS) was more susceptible to overt disease than another strain (P). The C3H and C57 strains appear to resemble the P strain in this respect.
5. Serial passage has activated latent MHV from the liver, kidneys, blood and faeces of apparently normal mice of the less susceptible P strain.
6. Infections with MHV were prevented by aureomycin and terramycin. Chloromycetin and sulphamerazine exerted a small effect; while penicillin and streptomycin exerted no effect under the conditions investigated.

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